PSJ17 Exh 102

DECEMBER 2011

Brought to You by

ANESTHESIOLOGY NEWS ClinicalOncology News PAINMEDICINE NEWS

Special REPORT

An Integrated Risk Evaluation and Mitigation Strategy for Fentanyl Buccal Tablet (*FENTORA*®) and Oral Transmucosal Fentanyl Citrate (ACTIQ®)

It is well recognized that the judicious use of opioids can facilitate effective and safe management of chronic pain. Nonetheless, the potential risks for misuse, abuse, addiction, and overdose must be considered when prescribing opioid medications. In an effort to manage the risks associated with all opioids, the FDA now requires a Risk Evaluation and Mitigation Strategy (REMS) for certain medications. A REMS is a regulatory program designed to improve the quality of medication use. It contains components that are intended to minimize the known or potential serious risks associated with a particular medication or therapeutic class and to ensure that the benefits outweigh those risks.

Rapid-onset opioids, including products such as fentanyl buccal tablet (*FENTORA*®) and oral transmucosal fentanyl citrate (OTFC; ACTIQ®), are important treatment options for opioid-tolerant patients with chronic cancer pain accompanied by breakthrough pain (BTP). Recently, the FDA adopted the more descriptive terminology of transmucosal immediate-release fentanyl (TIRF) for the class of rapid-onset opioids. Cephalon, Inc., is committed to maintaining access to appropriate pain management for the often debilitating effect of BTP in opioid-tolerant patients without compromising patient or public safety. Thus, Cephalon has implemented the recently FDA-approved ACTIQ and *FENTORA* REMS program to help mitigate potential safety concerns observed with opioids. Eventually, this approved REMS will be merged with REMS for other TIRF products to create a classwide program.

In this supplement, we present the background to the REMS program, a brief review of BTP along with the clinical data supporting the use of *FENTORA* and ACTIQ for BTP in appropriate opioid-tolerant patients, and an overview of the recently approved REMS for *FENTORA* and ACTIQ. Health care professionals who prescribe opioids will be required to enroll in the REMS program in order to prescribe these products.

McMAHON PUBLISHING

Supported by Cephalon, Inc.
Frazer, Pennsylvania

Although we understand that this may place an additional burden on those involved in prescribing, distributing, and dispensing TIRF products, we hope that these extra steps will ensure that these important medications are appropriately distributed to and received by the patients who need them.

The Steering Committee for ACTIQ® and *FENTORA*® REMS
Randy J. Bradway, MS, RPh; Bill Campbell; Claire Jurkowski, MD; Robert F. Kaper, MD; James Ottinger, RPh
Cephalon, Inc. Frazer, Pennsylvania

The Risk Evaluation and Mitigation Strategy: Background

James Ottinger, RPh
Susan Franks, MS
Cephalon, Inc.
Frazer, Pennsylvania

In 2007, the FDA Amendments Act provided the FDA with the authority to require pharmaceutical manufacturers to develop a REMS to ensure that the benefits of a drug outweigh its risks.[1] A REMS can be mandated for any newly approved prescription drug or biologic product or for any previously approved drug or biologic product if the FDA becomes aware of new safety information. In 2009, the FDA issued a draft "Guidance for Industry" outlining the format and content of a REMS program.[1] Each REMS is designed to minimize inappropriate use without hindering patient access to medications.[2] Currently, approximately 200 REMS programs have been approved by the FDA covering a wide variety of therapeutic areas, including opioid medications.[3]

REMS Components

A REMS program can have 5 components: (1) "Medication Guide" or patient package insert, (2) "Elements to Assure Safe Use," (3) communication plan, (4) implementation system, and (5) timetable for submission of assessment. Each REMS, however, does not have to encompass all of these components.[1]

The "Medication Guide" or patient package insert component of REMS serves as the primary educational tool for health care professional–directed patient education and is distributed to patients by the pharmacy at the time of dispensing.[1] Important elements of the "Medication Guide" include a description of the safety, including the adverse-event (AE) profile of the medication, warnings and precautions, storage requirements, and dosing.

The "Elements to Assure Safe Use" can include prescriber and pharmacist training and certification, restrictions on where the medication is dispensed, evidence of patient safe-use conditions, patient education, safety protocols, patient monitoring and enrollment or data collection forms, and medication monitoring procedures.[1] The mechanism by which these elements are disseminated is described in the communication plan. This component of the REMS may include letters to health care professionals or other stakeholders regarding medication risks and specific protocols to foster appropriate medication use.

In the implementation system, the drug manufacturer must take reasonable steps to monitor and evaluate the implementation of REMS by the stakeholders (eg, health care providers, pharmacists) who are responsible for executing its various REMS elements.[1] In the timetable for submission of assessment section, an assessment of the effectiveness of the REMS must be submitted to the FDA no less frequently than 18 months, 3 years, and 7 years after REMS approval.[1] This is the only component mandated for all REMS programs. The FDA may, at its discretion, require more frequent submission of REMS assessments.

REMS: Implications for Opioids

The use of opioid medications is an essential part of pain management for many patients with chronic pain. However, these medications have serious potential risks, including misuse, abuse, addiction, and overdose. For example, according to the most recent data available from the National Drug Intelligence Center and US Department of Justice, deaths caused by unintentional overdose involving prescription opioids increased 114% between 2001 (3,994 cases) and 2005 (8,541 cases).[4] In an effort to manage these risks, certain classes of opioids have been included in the federal mandate to develop a REMS.

In February 2009, the FDA contacted the manufacturers of all long-acting opioids (LAOs) and extended-release (ER) opioid formulations, including oxymorphone, oxycodone, morphine, methadone, transdermal buprenorphine, transdermal fentanyl, and hydromorphone, and mandated that the manufacturers design a classwide REMS program to accommodate all of these products.[2] To date, the FDA has approved several individual REMS programs for these opioid medications while the classwide REMS is being designed.[3] In April 2011, the FDA sent notification letters to all manufacturers of LAOs and ER opioids informing them of the need to submit a single-system REMS to provide training to health care professionals who prescribe opioids and to develop information for them to use when counseling patients about the risks and benefits of opioids.[5] Although specific medical education is not mandatory for prescribing ER opioids and LAOs in the REMS, separate legislation has been proposed in the US House of Representatives that would link mandatory training or certification to the Drug Enforcement Administration

registration number that already is required to prescribe controlled substances.[6]

In October 2010, the FDA contacted the manufacturers of TIRF products in order to harmonize individual TIRF-product REMS that were approved or under active review. In parallel, the FDA requested that the manufacturers work together to create a single, shared system for all TIRF products. In contrast to the REMS for LAOs and ER opioids, TIRF-product REMS programs contain a mandatory education element. A REMS meeting the new FDA requirements has been approved for the fentanyl buccal tablet (*FENTORA*) and OTFC lozenge (ACTIQ).[7] Cephalon, Inc., has launched a Web site, www.ReadyForREMS.com, to raise awareness of and provide updates to the REMS program and to serve as a resource for stakeholders looking for information about the FDA-mandated REMS for opioids. Additionally, REMS programs that meet the new FDA requirements are available for the fentanyl sublingual tablet (Abstral®) and fentanyl nasal spray (Lazanda®). Revisions to the existing REMS for fentanyl buccal soluble film (Onsolis®) are under review as of this writing.[3] To date, the FDA has not required REMS programs for non-TIRF, short-acting opioid products.

Breakthrough Pain in Cancer and Noncancer Patients: An Overview

Arvind Narayana, MD
Cephalon, Inc.
Frazer, Pennsylvania

Patients with chronic pain often experience transitory exacerbations of pain despite long-term treatment with an around-the-clock (ATC) opioid. These exacerbations, or flares, that occur on a background of otherwise well-controlled, persistent, chronic pain are defined as BTP.[8] BTP can escalate rapidly and unpredictably, reaching peak intensity within a median of 10 minutes.[9-12] The prevalence of BTP is high; in a recent survey of community-dwelling patients with chronic cancer pain or chronic noncancer pain (CNCP), 33% and 48%, respectively, experienced BTP.[11] The appropriate management of BTP is of particular clinical and socioeconomic importance. In patients with chronic pain who have controlled persistent pain, the presence of BTP has been associated with increased health care costs due to hospitalizations and emergency department visits,[13] and patients with BTP have greater functional impairment, disability, depression and anxiety, and decreased quality of life than patients without BTP.[10,14]

Physicians and other health care professionals caring for patients with pain often supplement the ATC opioid with short-acting oral opioids (eg, oxycodone, hydrocodone) for the management of BTP.[8,15,16] However, many BTP episodes reach peak intensity within minutes, far sooner than the onset of analgesia produced with conventional, orally administered, short-acting opioid medications (30-60 minutes),[9,10,16] thus limiting their therapeutic usefulness. TIRF products have been developed to address the need for opioids with a rapid onset of analgesia that more closely matches the time profile of a typical BTP episode.

Fentanyl Buccal Tablet: Clinical Data Review

The fentanyl buccal tablet is a rapid-onset, Schedule II opioid approved by the FDA in 2006 for the treatment of BTP in patients with cancer who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain.[17] Fentanyl buccal tablet uses OraVescent® drug delivery technology, which employs a chemical reaction to enhance the rate and extent of absorption of fentanyl through the buccal mucosa.[18] As a result, the pharmacokinetic profile of fentanyl buccal tablet is characterized by greater bioavailability and results in a higher early systemic exposure than OTFC and other fentanyl tablet formulations.[19-21]

The clinical efficacy and safety program for fentanyl buccal tablet encompasses 8 well-designed, peer-reviewed, published clinical studies. Three of these studies included patients with cancer-related BTP,[22-24] and 5 included patients with noncancer-related BTP (eg, neuropathic or low back pain).[25-29] An overview of these studies is summarized in the Table, and the analgesic response to fentanyl buccal tablet in these studies (as measured by the percentage of episodes of BTP with a ≥33% improvement in pain intensity [PI]) is presented in Figure 1.[30] In general, the inclusion and exclusion criteria in these studies are representative of the patient-selection standards that can be employed in clinical practice. Each study included opioid-tolerant patients who were receiving ATC opioids for their controlled persistent pain.[22-29] In some studies, patients had to have an average PI score of 6 or less (or in some studies, <7[23,25,29]) on a numeric rating scale ranging from 0 (*no pain*) to 10 (*worst pain imaginable*) for their chronic pain during the previous 24 hours to confirm that their persistent pain was reasonably well controlled.[23,25-29] Patients also had to report experiencing 1 to 4 BTP episodes per day that were at least partially relieved with a traditional short-acting opioid. Patients with a recent (within 5 years) history of alcohol or substance abuse or positive urine drug test for illicit substances were excluded.

Studies in Patients With Cancer

Two randomized, double-blind, placebo-controlled studies assessed the safety and efficacy of fentanyl buccal tablet

Table. Summary of Clinical Studies for Fentanyl Buccal Tablet

Study and Population Evaluated for Safety	Patient Population	Study Design	Primary Outcome Measure	Primary Results
Portenoy et al, 2006[22] (N=123)	Chronic cancer pain with BTP	Open-label titration followed by randomized, double-blind, placebo-controlled treatment phase	$SPID_{30}$ (fentanyl buccal tablet vs placebo)	LS mean (SE): 3 (0.12) vs 1.8 (0.18) *P*<0.0001
Slatkin et al, 2007[23] (N=125)	Chronic cancer pain with BTP	Open-label titration followed by randomized, double-blind, placebo-controlled treatment phase	$SPID_{60}$ (fentanyl buccal tablet vs placebo)	Mean (SE): 9.7 (0.63) vs 4.9 (0.50) *P*<0.0001
Weinstein et al, 2009[24,a] (N=232)	Chronic cancer pain with BTP	Open-label titration[a] followed by open-label maintenance phase of ≥12 mo	Safety assessments, including AEs, physical/neurologic examinations, and clinical laboratory tests	Most commonly reported AEs were nausea (37%), vomiting (22%), dizziness (20%), and fatigue (16%)
Simpson et al, 2007[25] (N=102)	Chronic neuropathic pain with BTP	Open-label titration followed by randomized, double-blind, placebo-controlled, crossover treatment phase	$SPID_{60}$ (fentanyl buccal tablet vs placebo)	Mean (SE): 9.63 (0.75) vs 5.73 (0.72) *P*<0.001
Portenoy et al, 2007[26] (N=104)	Chronic low back pain with BTP	Open-label titration followed by randomized, double-blind, placebo-controlled treatment phase	$SPID_{60}$ (fentanyl buccal tablet vs placebo)	Mean (SE): 8.3 (0.66) vs 3.6 (0.57) *P*<0.0001
Farrar et al, 2010[27] (N=148)	CNCP with BTP	Open-label titration followed by randomized, double-blind, placebo-controlled, crossover treatment phase	$SPID_{60}$ (fentanyl buccal tablet vs placebo)	Mean (SD): 7.7 (6.2) vs 4.6 (4.7) *P*<0.0001
Fine et al, 2010[29,a] (N=728)	CNCP with BTP	Open-label titration[a] followed by open-label maintenance phase of up to 18 mo	Safety assessments, including AEs, physical/neurologic examinations, and clinical laboratory tests	Most commonly reported AEs were nausea (17%), back pain (15%), vomiting (12%), and headache (11%)
Ashburn et al, 2011[28] (N=320)	Chronic cancer pain and CNCP with BTP	Open-label titration followed by randomized, double-blind, active-controlled, crossover phase	PID_{15} (fentanyl buccal tablet vs oxycodone immediate-release)	Mean (SD): 0.82 (1.12) vs 0.60 (0.88) *P*<0.0001

[a] This study enrolled patients who completed 1 of 2 previous double-blind, placebo-controlled, short-term studies. It also enrolled new patients who were being managed with around-the-clock opioids at time of enrollment but were naive to fentanyl buccal tablet.

AE, adverse event; **BTP,** breakthrough pain; **CNCP,** chronic noncancer pain; **LS,** least squares; **PID_{15},** pain intensity differences at 15 minutes; **SD,** standard deviation; **SE,** standard error; **$SPID_{30}$,** sum of pain intensity differences at 30 minutes; **$SPID_{60}$,** sum of pain intensity differences at 60 minutes

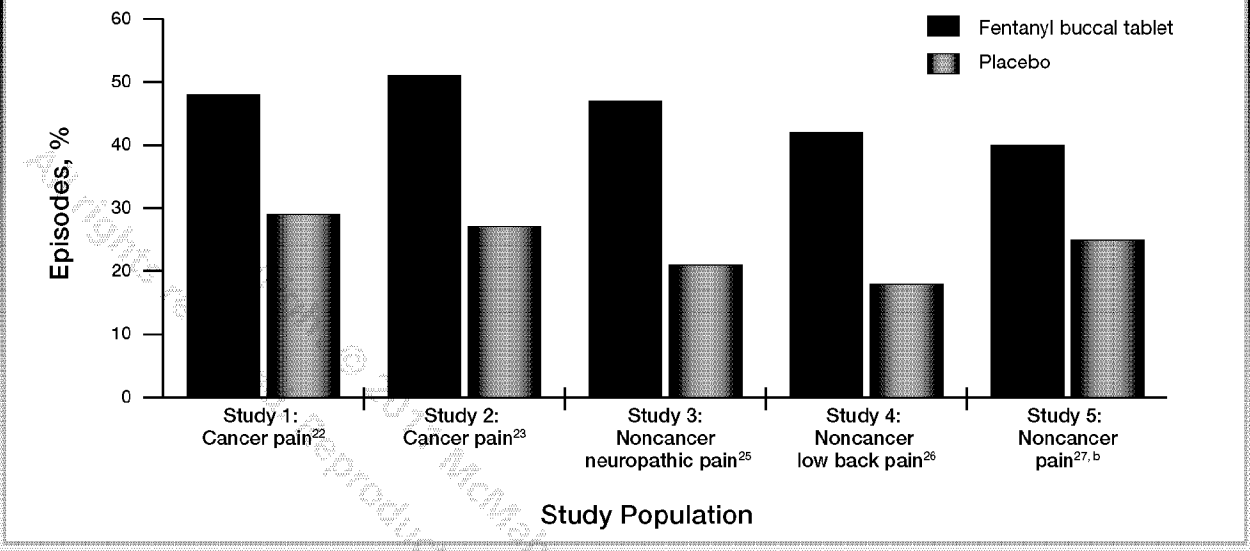

Figure 1. Percentage of BTP episodes with ≥33% improvement in PI at 30 minutes in randomized, double-blind, placebo-controlled, fentanyl buccal tablet studies.[a]

[a] All $P<0.05$, fentanyl buccal tablet vs placebo.
[b] During double-blind period 3.
BTP, breakthrough pain; **PI,** pain intensity
Adapted with permission from Fine et al, 2010.[30]

in opioid-tolerant patients with cancer.[22,23] After an open-label dose-titration phase, patients were then randomized to sequences of 10 tablets (7 fentanyl buccal tablet, 3 placebo) to treat 10 successive episodes of BTP. The sum of pain intensity differences at 30 minutes ($SPID_{30}$[22]) and 60 minutes ($SPID_{60}$[23]), the primary efficacy measures, was significantly greater for BTP episodes treated with fentanyl buccal tablet compared with placebo ($P<0.0001$) in both studies. PI differences also favored fentanyl buccal tablet in these 2 studies, with significant differences versus placebo seen as early as 10 to 15 minutes ($P<0.01$) and maintained through 1 to 2 hours ($P<0.01$).[22,23] AEs reported in 5% or more of patients in the 2 studies included nausea, dizziness, headache, fatigue, vomiting, constipation, asthenia, and somnolence.[31] Most AEs were typical of events observed with opioids, mild to moderate in intensity, and transient in nature. No incidents of respiratory depression or other serious AEs related to fentanyl buccal tablet were reported in either study.

Patients who completed either of these 2 studies were offered the option to enroll in a long-term (≥12 months), open-label extension study to assess the ongoing safety and tolerability of fentanyl buccal tablet.[24] This third study also enrolled new patients with cancer who were being managed with ATC opioids at study entry but were naive to fentanyl buccal tablet. As in the 2 short-term studies, the most frequently reported AEs in the extension study were of the type and severity typically observed in cancer patients treated with chronic opioid therapy. Only 1 study drug–related serious AE, drug withdrawal syndrome, was reported in this long-term safety study.

Studies in Patients Without Cancer

Of the 5 published studies of fentanyl buccal tablet that have been conducted in patients with CNCP, 1 study assessed the safety and efficacy of fentanyl buccal tablet for BTP in opioid-tolerant patients with chronic low back pain,[26] and another assessed fentanyl buccal tablet for neuropathic pain.[25] In these 2 studies, after an open-label titration phase, patients were randomized to treat 9 consecutive episodes of BTP (6 fentanyl buccal tablet, 3 placebo). Mean $SPID_{60}$, the primary efficacy measure, was significantly greater for BTP episodes treated with fentanyl buccal tablet than those treated with placebo ($P<0.001$) in both studies. Statistically significant differences in PI ($P<0.05$) also were observed as early as 10 minutes after administration of fentanyl buccal tablet, an effect that was maintained through 2 hours in these studies.

The third study consisted of 3 randomized, double-blind, placebo-controlled periods designed to assess the effectiveness of fentanyl buccal tablet in patients with CNCP over 12 weeks.[27] After completing a dose-titration phase, patients continued to a 12-week, open-label treatment phase, during which they received 6 doses of fentanyl buccal tablet

and 3 doses of placebo in a randomized sequence every 4 weeks. During the last of the 3 randomized treatment periods $SPID_{60}$, the primary efficacy measure, was significantly greater for fentanyl buccal tablet compared with placebo ($P<0.0001$). Differences in PI reached statistical significance at 15 minutes ($P<0.05$) and were maintained through 120 minutes. Additionally, a significantly higher proportion of episodes treated with fentanyl buccal tablet resulted in any pain relief beginning as early as 5 minutes after administration of fentanyl buccal tablet ($P=0.018$).

The fourth study assessed the safety and efficacy of fentanyl buccal tablet compared with immediate-release oxycodone in the treatment of BTP in opioid-tolerant patients with chronic cancer pain or CNCP.[28] After an open-label titration period during which patients identified successful doses of fentanyl buccal tablet and oxycodone, patients entered double-blind, randomized treatment period 1, during which they treated 10 BTP episodes with 1 of the 2 blinded study medications at the successful dose identified. During double-blind treatment period 2, patients treated 10 subsequent BTP episodes with the other blinded study drug. Significant differences in PI were observed as early as 5 minutes after fentanyl buccal tablet administration compared with oxycodone ($P=0.0081$) and were maintained through 60 minutes post dose ($P<0.0001$).

Patients who completed either of the first 2 noncancer studies were offered the option to enroll in a long-term (≥12 months), open-label extension study to assess the ongoing safety and tolerability of fentanyl buccal tablet.[29] This study also enrolled new patients with CNCP who were being managed with ATC opioids at study entry but were naive to fentanyl buccal tablet.

AEs in these 5 studies[25-29] were those typically observed in patients with CNCP treated with a potent opioid analgesic, and were similar to those observed in the studies that included patients with cancer and chronic pain with BTP. In a combined analysis of the 3 double-blind, placebo-controlled studies (Farrar et al,[27] Portenoy et al,[26] and Simpson et al[25]), the long-term, open-label extension study (Fine et al[29]), and an open-label, 4-week study in patients with chronic pain (Webster et al,[32] not presented here), the most frequently reported AEs (≥10%) were nausea, vomiting, dizziness, and headache.[33] Application-site reactions or abnormalities were reported in 12% of patients; these incidents tended to occur early in treatment, were transitory, and led to study discontinuation in approximately 1% of patients. Serious AEs that were considered possibly related or definitely related to study drug were reported in 2 of the 3 double-blind, placebo-controlled studies described earlier. One patient experienced accidental overdose resulting in a loss of consciousness.[26] This patient was admitted to the hospital and fully recovered. Another patient experienced pneumonia and had an accidental overdose of opioid medication, and in another patient, abuse of opioid medications resulting in withdrawal symptoms was reported.[27] During the long-term safety study, serious AEs occurred in 18% of patients, the most common of which included chest pain, pneumonia, and vomiting (5 patients each).[29]

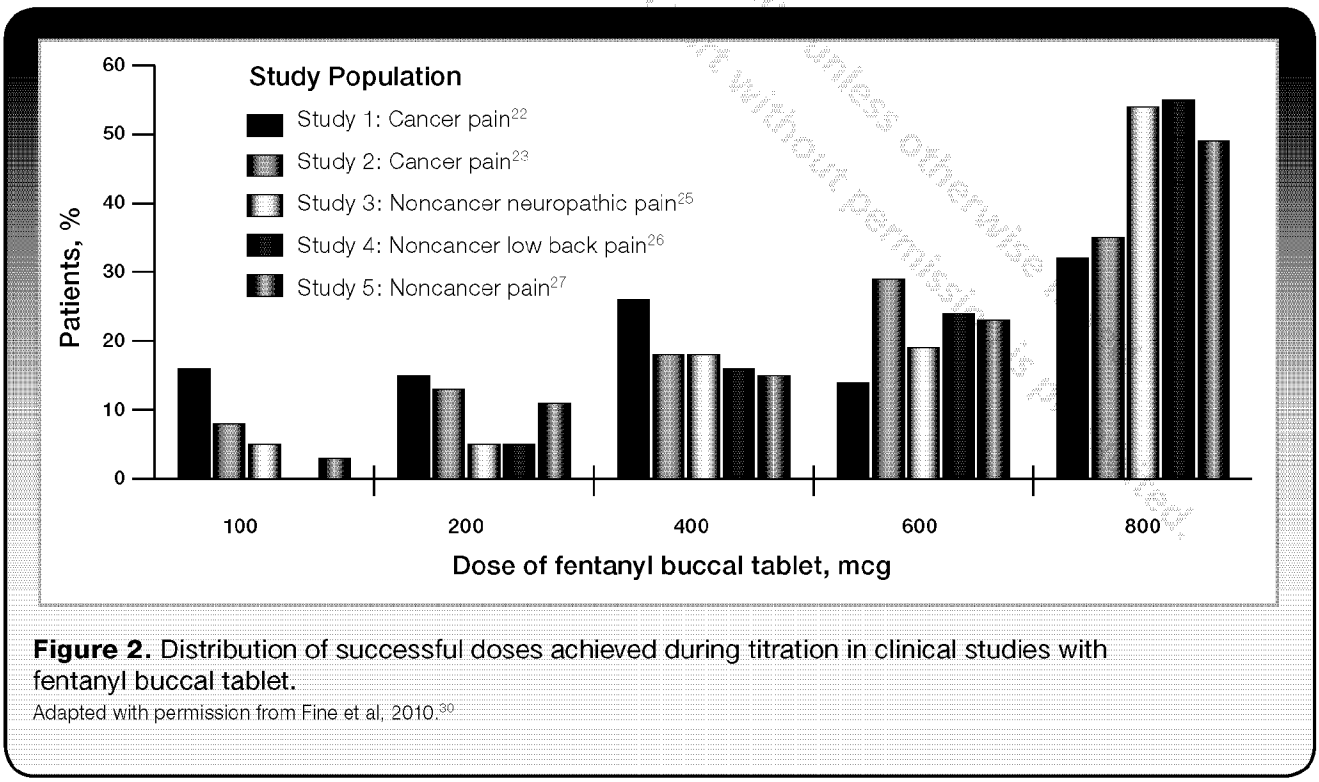

Figure 2. Distribution of successful doses achieved during titration in clinical studies with fentanyl buccal tablet.

Adapted with permission from Fine et al, 2010.[30]

Oral Transmucosal Fentanyl Citrate: Clinical Data Review

OTFC is a TIRF formulation approved by the FDA in 1998 for the treatment of BTP in patients with cancer who are already receiving and are tolerant to ATC opioid therapy for their underlying persistent cancer pain.[34] Each OTFC lozenge consists of fentanyl, incorporated in a sweetened matrix and attached to a handle. The patient administers OTFC by rubbing the lozenge along the inside of the cheek, which causes the lozenge to dissolve in the mouth, allowing rapid absorption of fentanyl through the buccal mucosa.[35]

The efficacy and safety of OTFC were assessed in a randomized, double-blind, placebo-controlled study of opioid-tolerant patients with cancer.[36] After an open-label titration period to identify an effective dose of OTFC, 92 patients entered a double-blind, crossover phase, where they were given 10 randomly ordered treatments (7 doses of OTFC at the effective dose identified and 3 placebo) in the form of identical lozenges to treat 10 BTP episodes. Significant differences in PI were observed at all time points after OTFC administration compared with placebo ($P<0.0001$). AEs were typical of those observed in patients with chronic pain and cancer treated with a potent opioid analgesic and included dizziness, nausea, somnolence, constipation, and asthenia. In addition, 2 randomized, open-label, dose-titration studies have assessed the use of OTFC for the treatment of BTP in opioid-tolerant cancer patients with persistent, chronic pain.[37,38] In these studies, 74% to 76% of patients with BTP successfully titrated to an effective dose of OTFC. AEs were typical of opioid-related events in both studies.

Patients successfully completing any of the 3 short-term cancer studies described earlier as well as new patients were eligible to enroll in a long-term, open-label extension study to assess the ongoing safety and tolerability of OTFC.[35] Rollover patients received OTFC at the effective dose determined in the short-term study. As expected, the most commonly reported AEs were typical of those reported with opioids (somnolence, constipation, nausea, dizziness, and vomiting). Six patients dropped out of the study due to an AE that was at least possibly related to OTFC.

Fentanyl buccal tablet has been shown to be effective in the treatment of BTP associated with multiple causes of pain. Nonetheless, TIRF products such as fentanyl buccal tablet and OTFC have been associated with potential risks for misuse, abuse, addiction, and overdose. According to an analysis of clinical studies of fentanyl buccal tablet in CNCP, 17% of patients had an aberrant behavior (eg, overadministration of study medication, medication theft, overdose), with 11% considered by the investigator to be possibly related to the study medication.[39] The incidence of aberrant behaviors in this study was low compared with previously published studies (32%-51%),[40,41] thus highlighting the importance of appropriately selecting patients who are most likely to benefit from treatment. It also is important to carefully titrate fentanyl buccal tablet and OTFC to identify the most appropriate dose for each patient to achieve acceptable analgesia without unacceptable AEs. In clinical studies of fentanyl buccal tablet, 65% to 81% of patients identified a successful dose, with the majority identifying a successful dose between 400 and 800 mcg (Figure 2).[30] Employing appropriate patient selection, treatment, and monitoring can help ensure that the benefits of fentanyl buccal tablet and OTFC treatment outweigh the risks.

REMS for ACTIQ and *FENTORA*

Randy J. Bradway, MS, RPh
Claire Jurkowski, MD
Robert F. Kaper, MD
James Ottinger, RPh
Cephalon, Inc.
Frazer, Pennsylvania

As part of its commitment to patient safety, and in compliance with the FDA guidance, Cephalon, Inc., has developed a REMS for ACTIQ (OTFC) and *FENTORA* (fentanyl buccal tablet). The goals of this REMS, which was approved by the FDA in July 2011, are to mitigate the risk for misuse, abuse, addiction, overdose, and serious complications resulting from medication errors by following the steps described here:

- Prescribing and dispensing *FENTORA* and ACTIQ only to appropriate patients (ie, only opioid-tolerant patients).
- Preventing inappropriate conversion between fentanyl products.
- Preventing accidental exposure to children and others for whom the medication was not prescribed.
- Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

The REMS integrates available technology to help ensure appropriate patient selection and education, checks and balances within the distribution channel, and dispensing of the medication for the appropriate, intended use. The ACTIQ and *FENTORA* REMS:

- Ensures that appropriate patients have access to their medicines while preserving availability at retail pharmacies.

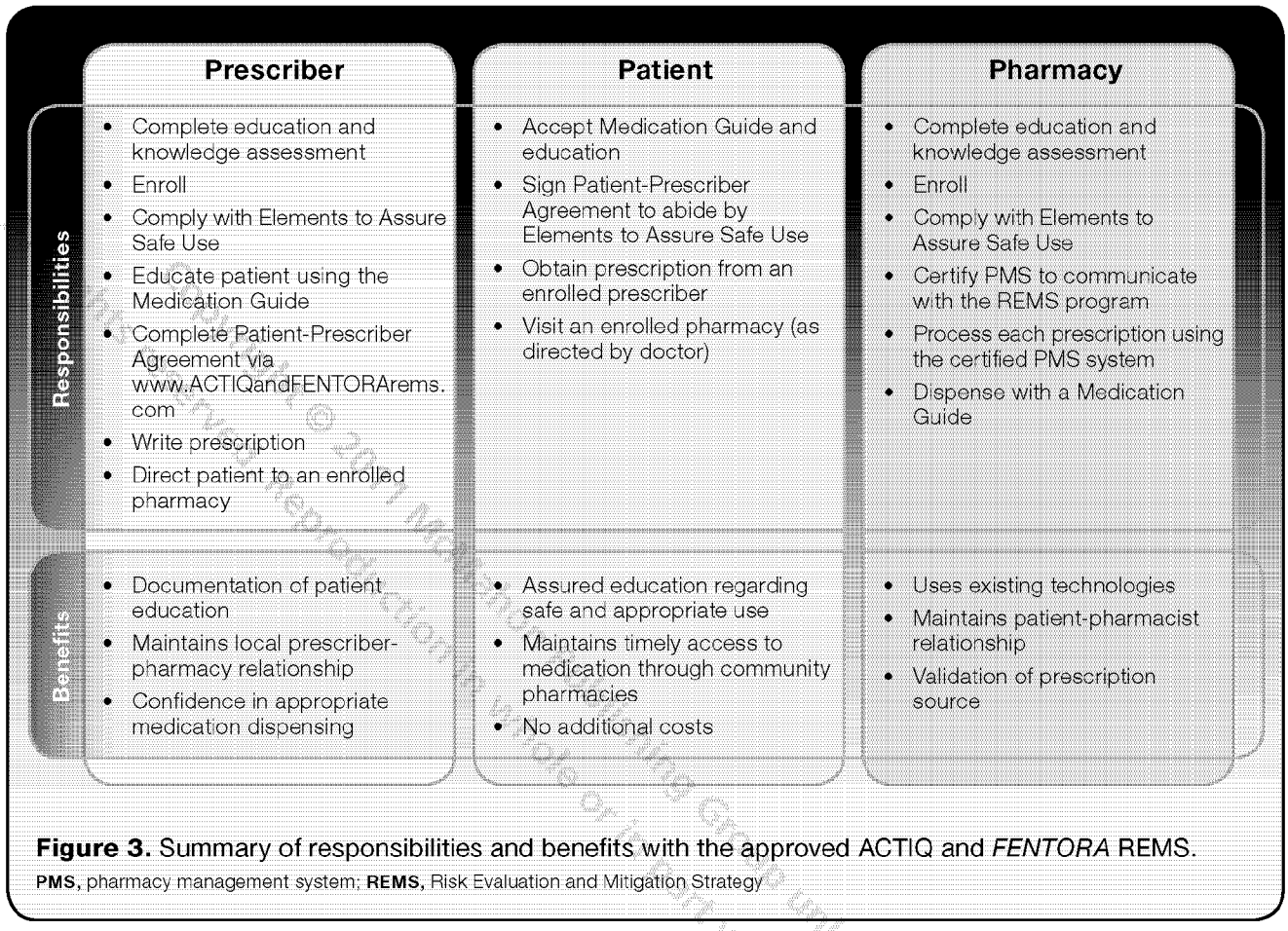

Figure 3. Summary of responsibilities and benefits with the approved ACTIQ and *FENTORA* REMS.

PMS, pharmacy management system; **REMS,** Risk Evaluation and Mitigation Strategy

- Enrolls prescribers and pharmacies through education about appropriate patient selection and additional key safety information in order for patients to receive medications they need.
- Enhances the dialogue about patient safety at the point of prescribing through required patient education about safe and appropriate use.
- Uses existing and familiar technology within the normal pharmacy stakeholder workflow to minimize disruption.

Elements of the approved ACTIQ and *FENTORA* REMS that will be most relevant to health care professionals are the "Medication Guide" and "Elements to Assure Safe Use" tools discussed earlier. The "Medication Guide" is an education tool for patients that contains specific product-related information such as administration guidelines, warnings and contraindications, AEs, and proper dosing written in easy-to-understand language for non–health care professionals. Health care professionals who prescribe these products will be responsible for reviewing the "Medication Guide" with, and providing a copy of it to, each patient at the time *FENTORA* or ACTIQ is prescribed, and pharmacists dispensing these products will be required to provide the guide to each patient with each prescription. The "Elements to Assure Safe Use" will require that *FENTORA* and ACTIQ be accessed through a single, closed system that requires stakeholders to complete specific education, assessment, and enrollment requirements (Figure 3).

Health care professionals who want to prescribe *FENTORA* or ACTIQ for outpatient use must enroll in the ACTIQ and *FENTORA* REMS program. Although prescriber enrollment is not required for inpatient use, it is required when health care professionals wish to prescribe *FENTORA* or ACTIQ upon patients' discharge. Health care professionals may enroll online by accepting the program's requirements and completing an education program and knowledge assessment and an enrollment form. Additionally, health care professionals must complete and sign a patient-prescriber agreement form for each new patient before the first prescription is written. This form confirms that the patient is opioid-tolerant and has been receiving ATC treatment with an opioid medication for more than 1 week. It also acknowledges that the health care professional has provided and reviewed the "Medication Guide" with the patient and that the patient has been informed about the risks, benefits, and appropriate use of *FENTORA* or ACTIQ. The patient also must sign the patient–prescriber agreement form.

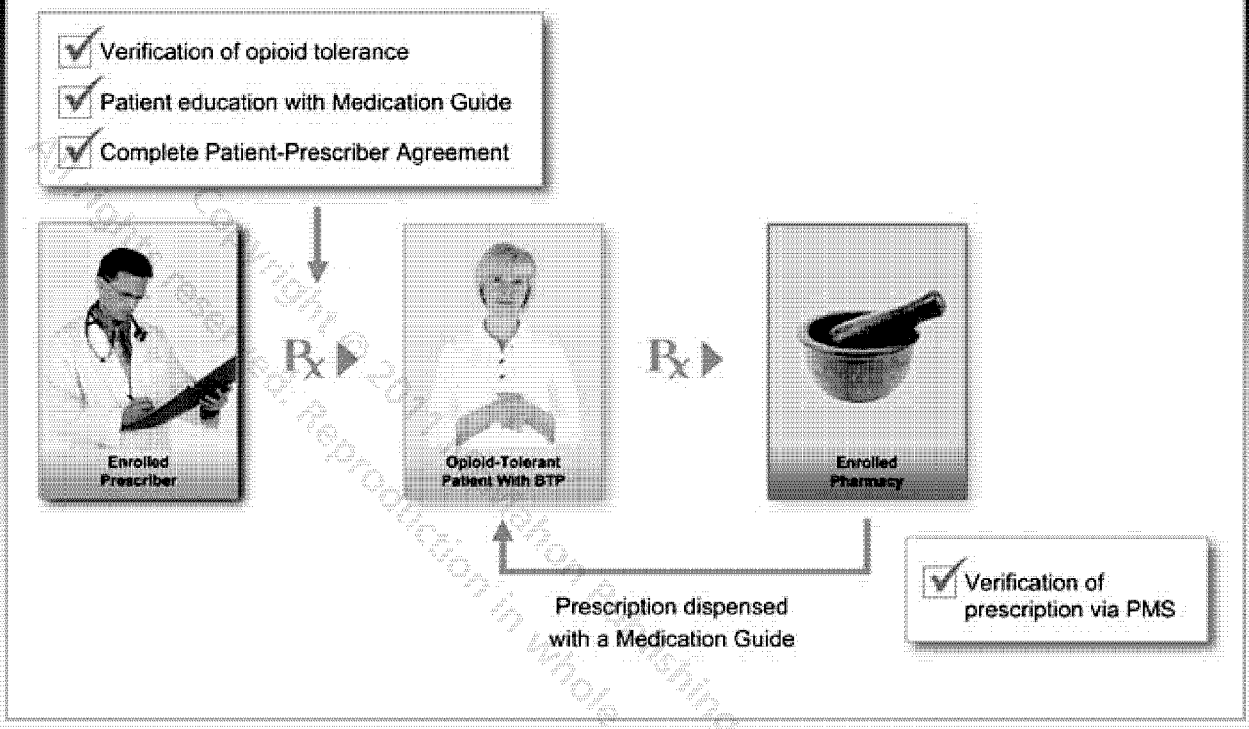

Figure 4. Medication prescription flow with the ACTIQ and *FENTORA* REMS.

BTP, breakthrough pain; **PMS,** pharmacy management system; **Rx,** prescription

Pharmacies must assign a designated pharmacist to complete a pharmacy-specific education program to train other pharmacy staff, a knowledge assessment, and an enrollment form. To ensure a controlled distribution model, the pharmacy will be eligible to purchase *FENTORA* and ACTIQ from enrolled distributors and dispense these medications to eligible patients only on completion of these steps. Furthermore, the existing pharmacy management system of enrolled pharmacies will be used to communicate with the REMS database. Through this communication channel, prescriber enrollment and completion of the patient–prescriber agreement form can be verified instantly. Prescription labels will be printed only once these conditions have been met. Enrollment in the ACTIQ and *FENTORA* REMS program may be completed online at www.ACTIQandFENTORArems.com. Enrollment must be renewed every 2 years or sooner in the event of major safety updates to the product labeling or major program changes.

The ACTIQ and *FENTORA* REMS program is a controlled, integrated system that is designed to ensure the safe and appropriate distribution, prescribing, and dispensing of these medications. Furthermore, the ACTIQ and *FENTORA* REMS program requires key stakeholders to work collaboratively (Figure 4). Doing so will help to enhance the dialogue between health care professionals and patients, preserve the local prescriber-pharmacy relationship, and coordinate patient counseling to support the safe use of *FENTORA* and ACTIQ.

According to provisions of the ACTIQ and *FENTORA* REMS, beginning March 2012, all stakeholders will need to be enrolled in order for a prescription to be filled. Cephalon, Inc., is also participating in the development of a classwide REMS for all TIRF products.[42] Although the specific details of this classwide REMS are under negotiation with the FDA, the system is likely to be similar to that of the recently approved ACTIQ and *FENTORA* REMS. Once it is approved, Cephalon, Inc., will work to ensure a smooth transition to the shared system while maintaining access to appropriate treatments for BTP in opioid-tolerant patients with cancer.

Acknowledgments

The clinical studies of fentanyl buccal tablet or OTFC mentioned in this supplement were sponsored by Cephalon, Inc. Writing support was provided by Peloton Advantage, funded by Cephalon, Inc.

References

1. Guidance for Industry. Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications: Draft Guidance. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2009.
2. Craig DS. The Food and Drug Administration risk evaluation and mitigation strategy. *J Pain Palliat Care Pharmacother.* 2010;24(2):145-148.
3. US Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsand-Providers/ucm111350.htm. Accessed July 6, 2011.
4. National Drug Intelligence Center, US Department of Justice. National Prescription Drug Threat Assessment 2009. Executive summary. Abuse. http://www.justice.gov/ndic/pubs33/33775/finance.htm#Abuse. Accessed July 19, 2011.
5. US Food and Drug Administration. Post-approval REMS Notification. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM251595.pdf. Accessed July 19, 2011.
6. Sullivan T. FDA opioid REMS: White House proposes mandated certified CME. Policy and Medicine. http://www.policymed.com/2011/04/fda-opioid-rems-white-house-proposes-mandated-certified-cme-.html. Accessed July 19, 2011.
7. Cephalon, Inc. Cephalon receives FDA approval for Risk Evaluation and Mitigation Strategy for FENTORA and ACTIQ. Press release. http://www.cephalon.com/media/news-releases.html?mode=year&reqid=1587678&ignore querystr=true. Accessed July 22, 2011.
8. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain.* 1990;41(3):273-281.
9. Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. *Pain.* 2003;101(1-2):55-64.
10. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain.* 1999;81(1-2):129-134.
11. Portenoy RK, Bruns D, Shoemaker B, Shoemaker SA. Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 1: prevalence and characteristics. *J Opioid Manag.* 2010;6(2):97-108.
12. Portenoy RK, Bennett DS, Rauck R, et al. Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain.* 2006;7(8):583-591.
13. Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain.* 2002;3(1):38-44.
14. Narayana A, Katz N, Shillington A, Portenoy R. The National Breakthrough Pain Survey (NBTPS): assessment of quality-of-life, functioning, and productivity [abstract 133]. *J Pain.* 2011;12(4 suppl):P9.
15. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.
16. Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. *Cancer.* 2002;94(3):832-839.
17. *FENTORA* [package insert]. Frazer, PA: Cephalon, Inc.; July 2011.
18. Durfee S, Messina J, Khankari R. Fentanyl effervescent buccal tablets: enhanced buccal absorption. *Am J Drug Deliv.* 2006;4(1):1-5.
19. Pather SI, Siebert JM, Hontz J, Khankari R, Kumbale R, Gupte S. Enhanced buccal delivery of fentanyl using the OraVescent drug delivery system. *Drug Deliv Technol.* 2001;1(1):54-57.
20. Darwish M, Tempero K, Kirby M, Thompson J. Relative bioavailability of the fentanyl effervescent buccal tablet (FEBT) 1,080 μg versus oral transmucosal fentanyl citrate 1,600 μg and dose proportionality of FEBT 270 to 1,300 μg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. *Clin Ther.* 2006;28(5):715-724.
21. Darwish M, Kirby M, Robertson P Jr, Tracewell W, Jiang JG. Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol.* 2007;47(3):343-350.
22. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain.* 2006;22(9):805-811.
23. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol.* 2007;5(7):327-334.
24. Weinstein SM, Messina J, Xie F. Fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic cancer pain: a long-term, open-label safety study. *Cancer.* 2009;115(11):2571-2579.
25. Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2007;29(4):588-601.
26. Portenoy RK, Messina J, Xie F, Peppin J. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. *Curr Med Res Opin.* 2007;23(1):223-233.
27. Farrar JT, Messina J, Xie F, Portenoy RK. A novel 12-week study, with three randomized, double-blind placebo-controlled periods to evaluate fentanyl buccal tablets for the relief of breakthrough pain in opioid-tolerant patients with noncancer-related chronic pain. *Pain Med.* 2010;11(9):1313-1327.
28. Ashburn M, Slevin KA, Messina J, Xie F. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. *Anesth Analg.* 2011;112(3):693-702.

29. Fine PG, Messina J, Xie F, Rathmell J. Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study. *J Pain Symptom Manage.* 2010; 40(5):747-760.

30. Fine PG, Narayana A, Passik SD. Treatment of breakthrough pain with fentanyl buccal tablet in opioid-tolerant patients with chronic pain: appropriate patient selection and management. *Pain Med.* 2010;11(7):1024-1036.

31. Zeppetella G, Messina J, Xie F, Slatkin NE. Consistent and clinically relevant effects with fentanyl buccal tablet in the treatment of patients receiving maintenance opioid therapy and experiencing cancer-related breakthrough pain. *Pain Pract.* 2010;10(4):287-293.

32. Webster LR, Messina J, Xie F, Nalamachu S. Effect of fentanyl buccal tablet on pain-related anxiety: a 4-week open-label study among opioid-tolerant patients with chronic and breakthrough pain. *J Opioid Manag.* 2011;7(4):297-308.

33. Nalamachu SR, Narayana A, Janka L. Long-term dosing, safety, and tolerability of fentanyl buccal tablet in the management of noncancer-related breakthrough pain in opioid-tolerant patients. *Curr Med Res Opin.* 2011;27(4):751-760.

34. ACTIQ [package insert]. Salt Lake City, UT: Cephalon, Inc. July 2011.

35. Payne R, Coluzzi P, Hart L, et al. Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain. *J Pain Symptom Manage.* 2001;22(1):575-583.

36. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst.* 1998;90(8):611-616.

37. Christie JM, Simmonds M, Patt R, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol.* 1998;16(10):3238-3245.

38. Portenoy RK, Payne R, Coluzzi P, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain.* 1999;79(2-3):303-312.

39. Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage.* 2011;41(1):116-125.

40. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res.* 2006;6:46-55.

41. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med.* 2005;6(6):432-442.

42. US Food and Drug Administration. FDA approves opioid analgesic to help cancer patients manage pain. Enrollment in REMS program required for health care professionals. FDA press release. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm239490.htm. Accessed July 12, 2011.

Disclaimer: This monograph is designed to be a summary of information. While it is detailed, it is not an exhaustive clinical review. McMahon Publishing neither affirms nor denies the accuracy of the information contained herein. No liability will be assumed for the use of this monograph, and the absence of typographical errors is not guaranteed. Readers are strongly urged to consult any relevant primary literature.

SR1140